REMARKS

Applicants submit herewith a Sequence Listing in computer readable form as required by 37 CFR §1.824. In addition, applicants submit an initial Sequence Listing as required under 37 CFR §1.823(a) and a statement under 37 CFR §1.821(f). Applicants respectfully request entry of the paper copy and computer readable copy of the Sequence Listing filed herewith for the instant application. The amendment to the specification merely inserts the paper copy of the Sequence Listing.

Applicants have amended claims 1 and 23. Support for the recitation "the first binding member is not labeled directly or indirectly" appears at page 8, lines 5-11 of the Specification, i.e., Example.[1] Support for the recitation "a second binding member of the binding pair is adapted for affixation on a solid substrate" can be found at page 9, lines 1-3 and lines 15-17. Applicants have amended the dependency of claims 32-36 and cancelled claim 37. No new matter has been added.

Upon entry of the amendments, claims 1-36 will be pending. Claims 10-22 have been withdrawn from further consideration as being drawn to non-elected inventions. Claims 1-9 and 23-36 are now under examination. Reconsideration of the application is respectfully requested in view of the following remarks.

Objection under 37 CFR 1.75

The Examiner objected to claims 3-5, 23, 26-28, and 30-31 as being substantial duplicates of claims 7-9, 29, 32-37. See the Office Action, page 2, lines 8-9.

The Examiner contended that claims 3-5 and claims 7-9 "cover the same thing" by referring to MPEP, Section 706.03(k),

> **When two claims** in an application are duplicates, or else are so close in content that they **both cover the same thing**, despite a slight difference in wording, **it is proper** after allowing one claim **to object to the other claim under 37 CFR 1.75 as being a substantial duplicate of the** allowed **claim**. See MPEP, Section 706.03(k).

[1] Two discrimination primers, R11-1-3mis18 (SEQ ID NO:2) and RM11-1-3mis18 (SEQ ID NO:3) were not labeled directly or indirectly. In contrast, the amplification primer, HjT-F8a (SEQ ID NO:1), was labeled with biotin at its 5'-terminus.

Claims 3-5 depend directly or indirectly from claim 2, which covers a discrimination primer having a segment with a length of 5-50 nucleotides. Claims 3-5 do not further limit the length of the segment. In contrast, claims 7-9 directly or indirectly depend from claim 6, which covers a discrimination primer having a segment with a length of 10-40 nucleotides. Claims 3-5, therefore, cover discrimination primers having lengths different from those covered by claims 7-9. In other words, claims 3-5 and claims 7-9 do not "cover the same things." Thus, it is not proper to object to claims 3-5 as being substantial duplicates of claims 7-9.

The Examiner also contented that claims 23 and 29 cover the same things. As claim 29 depends from claim 23, they do not cover the same thing. The objection should be withdrawn.[2]

Apparently, the Examiner believed that claims 26-30 are substantial duplicates of claims 32-36, respectively. Applicants have amended the dependency of claims 32-36. The scopes of claims 32-36, as amended, are different from those of claims 26-30, respectively. Claims 26-30 are therefore not substantial duplicates of the amended claims and the objection to them should be withdrawn.

Finally, the Examiner appeared to object to claim 31 as being a substantial duplicate of claim 37. Applicants have cancelled claim 37.

In view of the above comments and amendments, Applicants submit that the grounds for the objection have been overcome and request that the objection be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 27-28 and 33 as being indefinite. See the Office Action, page 3, lines 1-3. More specifically, the Examiner stated that the recitations "the first binding members of the first primers are different oligonucleotides" in these claims are not clear. The Examiner required Applicants to clarify what the first binding members are different from. See the Office Action, page 3, lines 4-6.

Applicants have disclosed in a working example two different first primers (discrimination primers), SEQ ID NOs: 2 and 3, each of which contains a binding member at its 5' end (i.e., "the first binding member" recited in the rejected claims). See page 8, line 8-11 of

2 In fact, the Examiner should have objected to claim 29 as being a substantial duplicate of original claim 35 since both claims depend from claim 23 and have similar recitations.

the Specification. The two binding members have different sequences (AGTTCTAGAGCGCTCGA vs. GAGTCGTATTACGGATCCT). As such, it allows one to distinguish two amplified nucleic acids by binding one of them to an address on a substrate and the other to another address on the substrate. See page 9, lines 1-14 of the Specification. In view of these teachings, one skilled in the art would understand that the recited "first binding members" are oligonucleotides having different sequences.

In view of the above remarks, Applicants therefore request withdrawal of this rejection.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected all pending claims being obvious on one or more grounds. Applicants respectfully traverse each of the grounds below.

I

Claims 1-2, 5-6, 9, 23-26, 28-29, 31-32, 34-35, and 37 were rejected as being obvious over U.S. Patent No. 6,156,503 to Drazen et al. ("Drazen") in view of U.S. Patent No. 6,383,742 to Drmanac et al. ("Drmanac"). See the Office Action, page 4, lines 1-2. Claim 37 has been cancelled. Applicants respectfully traverse the grounds for rejection and will discuss independent claims 1 and 23 first.

Claim 1, as amended, covers a discrimination primer for amplifying a nucleic acid that has a first base at a position suspected of a polymorphism and a second base immediately 3' to the first base. This discrimination primer has (1) a first nucleotide located at the 3' terminus of the primer and contains a base that is complementary to the first base; (2) a second nucleotide located immediately 5' to the first nucleotide and contains a base that is not complementary to the second base; (3) a segment of nucleotides located immediately 5' to the second nucleotide and is complementary to a part of the nucleic acid that is immediately 3' to the second base; and (4) a first binding member of a specific binding pair covalently bonded to its 5' terminus. The first binding member of the binding pair is not labeled directly or indirectly and a second binding member of the binding pair is adapted for affixation on a solid substrate.

This discrimination primer, together with an amplification primer that is labeled at its 5' end, allows one to amplify a polymorphism-containing target nucleic acid using a polymerase chain reaction (PCR). After the PCR, one can (1) affix one end of the amplified nucleic acid

onto a solid substrate via the first binding member and the second binding member already affixed on a substrate, and (2) detect the bound target nucleic acid via the labeled amplification primer incorporated into the other end of the amplified target nucleic acid. Note that the amplified target nucleic acid and the free discrimination primer can both bind to the substrate since they each contains a first binding member. The free discrimination primer, lacking a label, will not be detected. After the free labeled amplification primer is washed away from the substrate, only the amplified target nucleic acid can be detected by, e.g., an enzymatic reaction method. As one can minimize any background signals by washing away the free labeled amplification primer, one can therefore detect the amplified target nucleic acid at a high sensitivity. See page 2, lines 29-30 and page 7, lines 8-9 of the Specification.

Drazen teaches a method for identifying individuals who are likely to have negative responses to regular administration of β-agonists. This method requires an allele-specific PCR (column 1, lines 51-54), using a primer has a mismatch at its penultimate position. It detects an amplified nucleic acid by a conventional agarose gel/ethidium bromide-staining assay. See column 12, lines 3-6. Since ethidium bromide staining results in high background signals, this assay is far less sensitive than that disclosed by Applicants.

Drmanac teaches a method for detecting a target nucleic acid. This method includes forming a complex of a target nucleic acid, a labeled probe, and a probe affixed on a substrate. The labeled probe can be linked with one or more ligands that "serve as specific binding members to a labeled antibody, chemiluminescers, enzymes, antibodies which can serve as a specific binding pair member for a labeled ligand." See column 18, lines 64-67. The probe affixed on a support can be covalently linked to a microwell surface termed Covalink NH. See column 21, lines 59-60 and column 22, lines 1-14.

It is the Examiner's position that "[i]t would have been prima facie obvious to make the primer" of amended claim 1 by covalently binding the 5' end of a Drazen primer to a Drmanac ligand. The Drmanac ligand can be labeled directly with a chemiluminescer or enzyme or indirectly via an antibody. In other words, the combination of Drazen and Drmanac suggests a primer having a ligand that is labeled directly or indirectly. As discussed above, the discrimination primer of amended claim 1 has a first binding member that is not labeled directly or indirectly. To the extent that Drazen and Drmanac suggest a primer with a ligand that is

labeled directly or indirectly, they teach away from the discrimination primer of amended claim 1. As discussed above, in Applicants' method, it is the amplification primer, not the discrimination primer, that is labeled.

Amended claim 23 covers a kit that includes a discrimination primer of amended claim 1. It is therefore not obvious over Drazen in view of Drmanac for the same reasons set forth above. Neither are claims 2, 5-6, 9, 24-26, 28-29, 31-32, and 34-35, all of which depend from amended claims 1 and 23.

II

The Examiner further rejected claims 3-4, 7-8, 26, 30, 32, and 36 as being obvious over Drazen in view of Drmanac and U.S. Patent No. 5,994,056 to Higuchi et al. ("Higuchi"). See the Office Action, page 5, lines 7-10.

Higuchi teaches a method for nucleic acid detection using the PCR amplification. The method involves introduction of detectable DNA binding agents, such as dyes, into the amplification reaction to produce a detectable signal that is enhanced upon binding to double-stranded DNA. See the abstract. Higuchi also teaches primers having non-complementary sequences added to their 5' ends. These "tail sequences provide binding targets for specific dyes... and, consequently, [are] useful for increasing signal strength" of amplified DNA. See column 14, lines 38-47. In other words, Higuchi teaches primers having tail sequences that are labeled directly with dyes.

In contrast, the primer of amended claim 1 contains a first binding member that is not labeled directly. See the discussion in Part I above. In other words, like Drazen and Drmanac, Higuchi also teaches away from the primer of amended claim 1. Thus, Drazen, Drmanac, and Higuchi, alone or combined, do not render amended claim 1 obvious. Amended claim 23 covers a kit including a primer of amended claim 1. For the same reasons, it is not obvious over the cited documents. Neither are claims 3-4, 7-8, 26, 30, 32, and 36, all of which depend from amended claims 1 and 23.

COCLUSION

Applicants submit that the grounds for the rejection and objection asserted by the Examiner have been overcome, and that all pending claims define subject matter that is definite, non-obvious, and sufficiently described. On this basis, it is submitted that allowance of this application is proper, and early favorable action is solicited.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed.

Please apply any charges to Deposit Account No. 06-1050, referencing Attorney Docket No. 12674-003001.

Respectfully submitted,

Date: 3-4-03

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Version with markings to show changes made

In the specification:

Insert the paper copy of the Sequence Listing filed herewith following the Oath/Declaration.

In the claims:

Claim 37 has been cancelled.

Claims 1, 23, and 32-36 have been amended as follows:

1. A discrimination primer for amplifying a nucleic acid that includes a first base at a position suspected of a polymorphism and a second base immediately 3' to the first base, the primer comprising:

a first nucleotide, which is located at the 3' terminus of the primer and contains a base that is complementary to the first base;

a second nucleotide, which is located immediately 5' to the first nucleotide and contains a base that is not complementary to the second base;

a segment of nucleotides, which is located immediately 5' to the second nucleotide and is complementary to a part of the nucleic acid that is immediately 3' to the second base; and

a first binding member of a specific binding pair covalently bonded to the 5' terminus of the segment, wherein the first binding member is not labeled directly or indirectly and a second binding member of the binding pair is adapted for affixation on a solid substrate.

23. A kit for amplifying a nucleic acid that includes a first base at a position suspected of the polymorphism and a second base immediately 3' to the first base, the kit comprising a first primer and a second primer, wherein the first primer includes a first nucleotide, which is located at the 3' terminus and contains a base that is complementary to the first base, a second nucleotide, which is located immediately 5' to the first nucleotide and contains a base that is not complementary to the second base; a segment of nucleotides, which is located immediately 5' to the second nucleotide and is complementary to a part of the nucleic acid that is immediately 3' to the second base; and a first binding member of a specific binding pair covalently bonded to the 5' terminus of the segment, wherein the first binding member is not labeled directly or indirectly and a second binding member of the binding pair is adapted for affixation on a solid substrate.

32. The kit of claim 25 [24], wherein each of the first binding members of the first primers is, independently, a peptide or an oligonucleotide that is not complementary to any part of the nucleic acid.

33. The kit of claim 24 [26], wherein the first binding members of the first primers are different oligonucleotides.

34. The kit of claim 33 [27], wherein the second primer includes a label at the 5' terminus.

35. The kit of claim 31 [23], wherein the second primer includes a label at the 5' terminus.

36. The kit of claim 29 [23], wherein the first binding member is an oligonucleotide, which is not complementary to any part of the nucleic acid.